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Research Article

Maternal and fetal outcome in pregnancy with hepatitis E virus infection

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ABSTRACT

Background: Hepatitis E infection has been a major concern in the pregnant females due to its fulminant nature in pregnancy and increased mortality in pregnant females as compared the non-pregnant females and males. In spite of approximately 60 years of its discovery the cause of fulminant nature of hepatitis E in pregnancy still remains a mystery. The maternal and fetal outcomes are still unfavorable. Various studies and hypothesis have been given but still not proved. Hence the study was performed in tertiary care centre to evaluate the maternal and fetal outcome in pregnancy with hepatitis E virus infection.
Methods: All cases of hepatitis E, IgM positive visiting the antenatal clinic or admitted during the period of 2012 and 2014 at the tertiary care centre were included in the study. Other cases of hepatitis (noninfectious, other causes of viral hepatitis) were excluded. Maternal outcome in terms of acute liver failure, coagulation failure, hepatic encephalopathy and maternal mortality was studied. Fetal outcome in terms of, preterm labor, low birth weight, intrauterine fetal death was studied.
Results: In the study it was found that pregnant women with jaundice and acute viral hepatitis due to hepatitis E virus infection had a high mortality rate (52%), especially during third trimester and postpartum period (82%). The most common medical complication was coagulation failure (56%) and acute liver failure (27%) followed by hepatic encephalopathy (17%). The most common obstetric complication was post-partum hemorrhage (42%) followed by IUFD (24%), APH (8%).
Conclusions: The study shows that pregnant women with jaundice and acute viral hepatitis due to hepatitis E virus infection had a high mortality rate especially during third trimester and postpartum period and also they had poor obstetric and fetal outcome.

Keywords: Hepatitis E virus, Jaundice, Maternal mortality

INTRODUCTION

Every year there are an estimated 20 million hepatitis E infections, over 3 million acute cases of hepatitis E and 56,600 hepatitis E-related deaths.[1] Enteric ally transmitted hepatitis E virus is the most frequent cause of acute viral hepatitis in developing countries.[2] Hepatitis E can occur either in large epidemics or in small sporadic cases. Secondary attack rate is more during epidemic as compared to sporadic.[3]

Hepatitis E is found worldwide, but the prevalence is highest in East and South Asia. HEV infection is the most frequent cause of acute sporadic and epidemic hepatitis in India.[3] Outbreaks of hepatitis E are more common in parts of the world with hot climates and are rare intemperate climates. Outbreaks are mainly associated with faecal contaminated drinking water; exceptions are food-borne epidemics (raw or uncooked shellfish). The first epidemic in India was at Delhi between December 1955 and January 1956.[2] It took 30 years to recognize it as a different virus when the sera from persons during the

two waterborne epidemics were negative for hepatitis A and B.[4,5]

HEV is a non-enveloped, spherical, 7.5 kb, positive stranded RNA genome with 3 open reading frames (ORFs).[6,7] Although originally classified within the family of caliciviruses, but now they are classified within family hepeviridae.[5] The virus was first isolated in 1980s.

HEV is classically transmitted feco-orally (food borne, waterborne), although person-to-person transmission has also been reported. HEV has been occasionally linked to nosocomial spread. Vertical transmission from mother to infant is also known to occur. It is infrequently transmitted by transfusion of blood or blood products.[8,9] Incubation period following exposure to hepatitis E virus is 3-8 weeks with a mean of 40 days.

HEV has an interesting course in pregnant women. Studies have shown that incidence of incidence of HEV infection in pregnancy is high and a significant proportion can progress to fulminant hepatitis. Pregnant woman particularly in second and third trimester are affected more frequently during epidemics with mortality rate of 5-25% as compared to general population 0.06%-12%. The occurrence of acute liver failure is about 10-22% as compared to 1-2% in general population.[4,10] Sporadic hepatitis E is also associated with increased incidence and severity in pregnant women.[10]

There is increased chance of maternal complications like ante partum haemorrhage, postpartum haemorrhage, premature rupture of membrane, IUFD, medical complication like coagulation failure (DIC), hepatic encephalopathy. Fetal complications like preterm, abortions, still births, low birth weight. The increased severity of hepatitis E infection in pregnancy is attributed to various factors like hormonal changes during pregnancy (steroid hormone directly influence virus replication), reduced immune response during pregnancy, malnutrition, but are still under evaluation. There is unusual behaviour of hepatitis e in pregnancy. Therefore, this study is undertaken to study the maternal and fetal outcome in sporadic cases.

METHODS

Observational prospective study was done at department of obstetrics and gynaecology at tertiary care centre for 2 years. All pregnant women with positive HEV IgM antibodies were included in the study. Other causes (non-infective) of liver diseases in pregnancy were excluded in the study. 50 cases were studied.

Study procedure

All patients visiting the antenatal outpatient department or admitted, with HEV IgM positive, were subjected to detailed history taking regarding present history like maternal age, gravidity, parity, gestational age based on last menstrual period and past history. If the patient is clinically suspected of having jaundice serological tests for infective hepatitis E was done. If the patient is found positive for HEV will be included in the study. Follow up of the patients was done. Intrapartum; mode of delivery and post-partum maternal complications were noted. Fetal outcome was observed.

Study analysis

Data analysis was computer based. Data entry sheet was designed in computer software and statistical analyses were performed by using Statistical Package for the Social Sciences software version 16.0 (Chicago IL, USA). Variables of interest were age, gestational age at presentation, fetal and maternal outcome.

Quantitative variables such as age, gestational age, laboratory parameters were analyzed using simple descriptive statistics like mean and standard deviation. Qualitative variables such as, fetal and maternal outcome were calculated using frequency and percentage.

RESULTS

Followed by 32% belong to the age group 26-30 years, 16% belong to the age group of less than 20 years and the minimum age group was more than 30 years 8%.

Table 1: Distribution of study group as per age.

Age	Frequency	Percent
Upto 20 years	8	16.00%
21 to 25 years	22	44.00%
26 to 30 years	16	32.00%
More than 30 years	4	8.00%
Total	**50**	**100.00%**

In the study group maximum patients belong to the third trimester; 50% were between 24-36 weeks of gestation followed by 32% in more than 36 weeks and 18% in 12-24 weeks. No patient was found in the first trimester. The mean gestational age was 31.21 and minimum gestational age was 14 weeks and maximum was 40.2 weeks.

Table 2: Distribution of study group as per period of gestation (POG).

POG	Frequency	Percent
12 to 24 weeks	9	18.00%
24 to 36 weeks	25	50.00%
>36 weeks	16	32.00%
Total	**50**	**100.00%**

In the study group the mean haemoglobin was 9.37 with maximum of 12 g% and minimum of 6 g%.

Table 3: Laboratory parameters.

Statistics	N	Mean	Std. dev	Median	Minimum	Maximum
	50	9.37	1.24	9.50	6.00	12.00
Hb	50	13,244.00	4,930.79	12,450.00	6,000.00	30,000.00
TLC	50	2.16	0.71	2.16	0.50	3.56
Plt (lakhs)	50	10.54	4.81	9.90	2.80	22.40
T.BIL	50	360.70	331.54	251.00	40.00	1,200.00
SGOT	50	471.80	404.99	414.00	40.00	1,600.00
SGPT	50	26.10	10.19	29.00	16.00	44.00
PT	50	1.91	0.82	1.74	1.00	3.50
INR						

Table 4: Haemoglobin level distribution among the study group.

Haemoglobin (g %)	No .of patients
<7	2
7-10	34
>10	14

The mean total bilirubin was 10.54 which range was 2.80 to 22.40.

Table 5: Distribution of total bilirubin among the study group.

Total bilirubin	No. of patients
<2	0
2-6	10
6-12	20
12-18	17
>18	3

The SGOT was found to be in range of 40-1200IU/ml with mean value as 360.70, mean SGPT was 471.80 and range 40-1600. In the study group the prothrombin time was between 16 to 44 and the mean was 26.10.

The mean INR was 1.91 and maximum value of INR was 3.50 and minimum value was 1.

Table 6: Distribution of INR among study group.

INR	No. of patients
<1.5	22
>1.5	28

The medical complications were found to be mainly coagulation failure (CF) (INR .1.5 with bleeding tendencies and DIC) in 28/50 patient i.e. 56% of cases.

The next most common complication was found as acute liver failure (ALF) (coagulation failure with hepatic encephalopathy within 8 weeks of illness) in 19/50 patients i.e. 38%. The third medical complication was hepatic encephalopathy (HE) was found in 17/50 patients i.e. 34%.

Table 7: Distribution of study group as per medical complication.

Medical complications	Frequency	Percent
CF	28	56.00%
ALF	19	38.00%
HE	17	34.00%

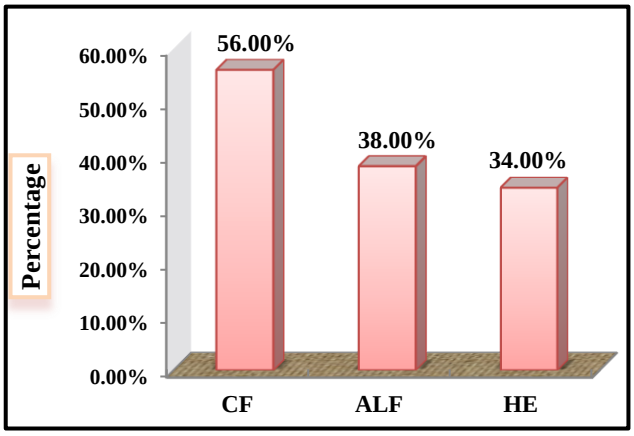

Figure 1: Distribution of study group as per medical complication.

The obstetric symptoms were mainly ante partum haemorrhage, post-partum haemorrhage, IUFD, premature rupture of membrane and abortion.

The most common obstetric complication was post-partum haemorrhage, 21/50 i.e. 42%. Most of the patients with postpartum haemorrhage were managed by medical management and if required transfusion of blood and blood products like fresh frozen plasma.

Ante partum haemorrhage was seen in 4/50 patients which makes 8%.the other complication was intrauterine fetal death which was present in 12/50 cases i.e. 24 %.

The other obstetric complication was premature rupture of membrane in 6% cases and abortion in 12% cases.

The above indicates individual complication but patient in the study group had multiple complications at the same time, like PPH with IUFD occurred in 6 cases, abortion with PPH occurred in 2 cases. All the patients with post partum haemorrhage required blood transfusion as well as fresh frozen plasma.

Table 8: Distribution of study group as per obstetric complications.

Obstetric complication	Frequency	Percent
APH	4	8.00%
PPH	21	42.00%
IUFD	12	24.00%
PROM	3	6.00%
Abortion	6	12.00%

Most of the patients in the study group delivered vaginally 31/50 i.e. 62% no patients required instrumental deliveries. There were 5 patients requiring lower segment caesarean section which makes 10% .The indication of LSCS were meconium stained liquor -2, breech presentation-2, non-progress of labor-1. One patient who underwent caesarean section expired. 1 patient required obstetric hysterectomy post LSCS in view of post-partum haemorrhage the mother was discharged with healthy baby.

4 patients of LSCS were given blood and fresh frozen plasma both pre and post operatively and one received only preoperatively. 8/50 patients did not deliver and 6 patients aborted spontaneously.

Table 9: Distribution of study group as per, mode of delivery.

Mode of delivery	Frequency	Percent (%)
LSCS	5	10.00
VD	31	62.00
ND	8	16.00
Abortion	6	12.00
Total	50	100.00

It was found that 26/50 patients expired i.e. 52%, and 24/50 i.e. 48% patients were discharged. The total maternal mortality at our tertiary care centre due to various causes in the study period was 88. The deaths due to hepatitis E virus 26. The percentage of deaths due to hepatitis E infection was -29.54%

Therefore if we calculate the maternal mortality rate (maternal deaths within 42 days/total live births*100000) the total maternal mortality rate comes to be 1217.17 per one lakh live births in our the tertiary care hospital, that due hepatitis E comes to be 359.61.

Table 10: Distribution of study group as per, maternal outcome.

Maternal outcome	Frequency	Percent
Discharge	24	48.00%
Expired	26	52.00%
Total	**50**	**100.00%**

In the study group it was found that total 36 patient delivered 8 patient did not deliver and 6 patient aborted. Out of 36 patient delivered 12 were preterm that is patient delivered before 37 weeks of gestation, 2 deliveries were very low birth weight (<1.5kg) and rest 10 were low birth weight babies (1.5-2kg). 3 patients delivered babies which were low birth weight for that gestational age (below 10th percentile for its gestational age) i.e. IUGR now termed as fetal growth restriction.

All low birth weight and IUGR babies were admitted in neonatal intensive care unit. 6 babies developed necrotizing enterocolitis during NICU stay. 4 babies admitted in the NICU expired and rest were discharged healthy. 11 patients delivered normal healthy baby which makes 30.56%. In the study group it was found that 10 patient delivered still birth i.e. 27.78% babies out of which 6 were macerated still birth(decided by the paediatrician on the basis of duration of IUFD usually >24 hours with sign of maceration) and 4 were fresh still births.

Table 11: Distribution of study group as per, fetal outcome.

Fetal outcome	Frequency	Percent
IUGR	3	8.33%
LBW(Preterm)	12	33.34%
Normal healthy baby	11	30.56%
Stillbirth	10	27.78%
Total	36	100.00%

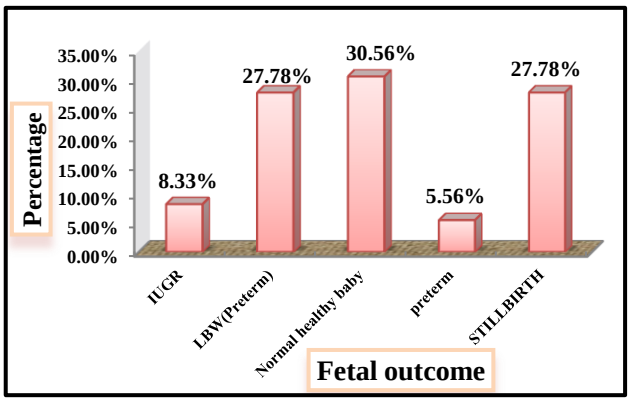

Figure 2: Distribution of study group as per fetal outcome.

Table 12: Comparison between discharged and expired in relation to POG and laboratory parameters.

Study parameter	Discharge				Expired				
	N	Mean	SD	Median		N	Mean	SD	Median
Pog	24	33.43	6.40	36.00	pog	26	29.16	7.08	28.95
Hb	24	9.81	0.96	10.00	Hb	26	8.96	1.35	9.15
T.BIL	24	7.70	3.90	6.35	T.BIL	26	13.17	4.06	13.20
SGOT/AST	24	168.00	211.19	77.00	SGOT	26	538.58	325.35	500.00
SGPT/ALT	24	247.92	313.07	115.50	SGPT	26	678.46	372.52	526.00
INR	24	1.27	0.37	1.11	INR	26	2.51	0.65	2.55

The above table and graph compares the laboratory parameters in the expired group and the discharged group. The mean haemoglobin level in the expired group was found to be 8.96 as compared to the discharged group in which it was found to be 9.81 g%.

The mean total bilirubin level in expired group was found to be 13.17 mg% as compared to the discharged group were it was 7.70 mg%, thus the bilirubin level was significantly higher in the expired group. The mean SGOT/AST level in the expired was found to be 538.0 U/L as compared to the discharge group were it was found to be 168.0 U/L which was significantly lower.

The mean INR in the discharge group was found to be 1.27 as compared to the expired group were it was found to be 2.51 which were significantly higher. This shows that the laboratory parameters in the expired group were more deranged than the discharge group, thus earlier detection might change the prognosis of the disease.

DISCUSSION

Gravid status and period of gestation

We observed that 50% patients were primigravida and 50% patients were multigravida. Median gestational age was 31.2weeks and 82% cases were in 3rd trimester of pregnancy. Nearly 18% of cases were in 2nd trimester. This observation is similar to previous studies, which showed increasing incidence as gestational age increases. The relation between gravid status and incidence was not studied in previous studies.

Various other studies found that majority of patients presented in third trimester and also the incidence of fulminant hepatic failure and maternal mortality was more in third trimester as compared to second and first trimester (Yasmeen et al, Shrestha et al, Khruoo MS et al, Brohi et al).[13,14,16]

Laboratory parameters

Liver function tests indicate hepatic necrosis. Laboratory test abnormalities include rise in serum bilirubin mostly conjugated, marked rise in serum aminotransferases, gamma glutamyl amino transferase (GGT) and serum alkaline phosphatase (SAP) activities. A rise in aminotransferase levels may be before the onset of symptoms by as long as ten days and reaches a peak by the end of first week. As illness subsides, serum transaminase and bilirubin abnormalities start declining, reaching normal values by 6 weeks in most patients.[17]

Table 13: Gravid status.

Study	Primigravida	Multigravida
Sultana et al[11]	40%	60%
Shinde et al[12]	71%	29%
Current study	50%	50%

Table 14: Period of gestation comparison.

Study	First trimester	Second trimester	Third trimester	Mean gestational age (weeks)
Shrestha et al[13]	5%	4%	91%	31
Brohi et al[14]	11.5%	7.6%	80.76%	31
Sultana et al[11]	Nil	4%	96%	
Shinde et al[12]	3.8%	32.6%	67.3%	27.5
Patra et al[15]	Nil	33%	67%	31
Khuroo et al[16]	-	-	67%	27.2
Current study	Nil	18%	82%	31.2

Clinical studies have shown that the elevation of serum ALT levels occurs as a single peak preceding or coinciding with the onset of jaundice, which is similar to most of the other forms of viral hepatitis.[18]

The mean total bilirubin levels in our study were 10.54 and the bilirubin range was 3-22. Also the serum transaminases were raised mean SGOT and SGPT levels were 360 and 471 respectively. The mean INR 1.91.

The study conducted by Patra et al showed mean total bilirubin levels as 15, mean alanine transaminases as 90.5, mean prothrombin time as 58, mean INR 4.[15]

In a study conducted by Xu B et al, found that HEV infected patients with severe jaundice had significantly lower peak serum levels of γ-glutamyl-transpeptidase, low albumin levels, low acetylcholine esterase level, high total bile acid levels, high viral load and longer hospital stay than those without severe jaundice.[19]

Medical complications and obstetric complications

Medical complications

In our study we found medical complications as coagulation failure (56%), hepatic encephalopathy as (17%) and acute liver failure which is defined as development of hepatic coagulopathy and encephalopathy within 8 weeks of onset of symptoms, was in (19%). The patient with medical complications were admitted in medical intensive care unit and managed by obstetricians and physicians both, most of the patients were allowed to go in spontaneous labour, induction of labour was not preferred.

The study conducted by Shinde et al showed that encephalopathy was the most common complication of HEV infection in pregnancy. Another study conducted by Shrestha et al had 24% cases of acute liver failure, 52% of coagulation failure and 8 % acute renal failure. Patra et al found 79% of coagulation failure and 74% acute liver failure.

Study conducted by mufti et al showed hepatic encephalopathy and coagulopathy as most common medical complication in hepatitis e. Khuroo et al also found that among 62 patient which were studied hepatitis e caused fulminant hepatic failure in 81% of cases.[16]

Thus similar to various studies we also found coagulopathy and acute liver failure in our patients as most common complications which was significant and the severity increased after the delivery.

Obstetric complications

We in our study found that post-partum haemorrhage was the most common obstetric complication 21/50 i.e. 42% followed by IUFD 24%, APH 8% and PROM 3%.In various other studies also similar results were found like Shrestha et al found 27% post-partum haemorrhage which was most common symptom followed by 4% ante partum haemorrhage and 5% intrauterine fetal death. A study conducted by Patra et al found ante partum haemorrhage 23% and intrauterine fetal death 58% as most common symptoms followed by post-partum haemorrhage 14% and premature rupture of membrane 9%.[15]

Patra et al also concluded that women with hepatitis E infection in pregnancy as compared to other viral hepatitis are more likely to have obstetric complications like ante partum hemorrhage, post-partum haemorrhage, intrauterine fetal death.[15]

Mode of delivery

In the present study it was found that most of the patient delivered vaginally i.e. 62% and 10% i.e. 5 patient had to undergo lower segment caesarean section, rest were either abortion or did not deliver. The preferred mode of delivery was vaginal delivery as there not much consensus and study about mode of delivery various studies have found vaginal delivery as most common, caesarean section is done very rarely due to increased chances of morbidity.[15]

Maternal outcome

Listed below are the various study conducted allover India over the years and the percentages of maternal mortality and the range is from 19-73%.

Rein et al recently published their estimates of the global incidence of HEV infections and associated deaths in the year 2005, which suggested that >20 million infections and 3.3 million cases of hepatitis E per year, and a 20% probability of death in pregnant women infected with hepatitis E virus.[20]

Table 15: Maternal mortality (HEV infection in pregnancy) in various previous studies.

Study	Maternal mortality (%)
Hussain et al[21]	20
Jaiswal et al[22]	56
Singh et al[23]	64
Khuroo et al[16]	55
Beniwal et al[24]	39.1
Shrestha et al[13]	19.35
Banait et al[25]	12
Kumar et al[26]	73
Patra et al[15]	41

In our study we found that that maternal mortality rate was 26/50, i.e.52 %. The total number of maternal deaths in our tertiary care centre in the study period was 88 and that due to hepatitis E in pregnancy is 26.Thus the

percentage of deaths due to hepatitis E is 29.54% which is significant.

In endemic countries, acute hepatitis E in pregnant women can lead to spectrum of hepatic dysfunction from acute liver failure to decompensation of liver cirrhosis and it is associated with 80% mortality despite the best possible care.

The reasons of fulminant course for hepatitis e in pregnancy have been studied by various researchers but there is no one consensus. Jilani et al found that HEV infected pregnant women with fulminant hepatic failure had lower CD4 count and higher CD8 counts.

Pal et al studied the cellular immune response in both pregnant and non-pregnant women with acute hepatitis E and the control population found that pregnant women with HEV had generalized immune suppression characterized by decrease in lymphocyte response to phytohemagglutinin (PHA) with a predominant Th2 bias as compared to non-pregnant women with hepatitis E and normal healthy controls.[27]

Navneethan U et al hypothesized that the difference in the genotype or its subtypes of the Hepatitis E virus infection could be the answer.[28]

In addition to the above mentioned factors, Khuroo et al suggested that infection of the foetus with HEV may be responsible for the increased severity of the disease in the mother.[4]

Devhare et al. studied the immune response to HEV infection and observed early cellular response in HEV infection and associated molecular mechanisms suggesting the potential role of the inflammatory response triggered by HEV infection in host immune response and pathogenesis.[29]

Tripathy et al. found that elevated IL-1 α and sIL-2 receptors α (sIL-2R α) level in the blood are pivotal in the pathogenesis of HEV. They also demonstrated involvement of innate immune response at the site of infection.[30]

Furthermore, Srivastava et al. suggested that interferon-γ secreting CD4 lymphocytes are involved in immune response and are related to intrahepatic sequestration of immune response.[31] All these studies suggest that the immune mediated destruction of hepatocytes is important in the pathogenesis of hepatitis E.

The mechanism of liver injury in hepatitis E is not clear and all the hypotheses put forth has not been yet conclusively proved. In this situation of uncertainty, the management of HEV infection induced liver failure assumes more importance than ever before. All the studies have shown that pregnant women have the differential immune response which triggers fulminant liver failure. So the logical treatment should be to deliver the fetus as soon as possible. Unfortunately, very few such studies have been undertaken in this field. Also some study shows including current study that condition deteriorated and maternal mortality high after delivery while some study like by Banait et al suggested no difference so still the situation remains unclear about management.[25]

Fetal outcome

In our study it was found that 36/50 delivered remaining 14, 8 patient did not deliver and 6 were aborted. Out of 36, 12 were preterm deliveries i.e. 33% f/b 11 (30.5%) were normal healthy baby, 3 (8.33%) were intrauterine growth retardation and 10 (27.78%) still birth. Most of them delivered normally (31) followed by 5 patient had under gone caesarean section by lower segment caesarean section.

Previous studies Shrestha et al out of 79 delivered, 56 preterm and 26 full term,20% perinatal mortality, 11% still births.[13] Patra et al had 90% preterm deliveries, 54% still births, 17%neonatal deaths ,21%live births. There were 69% fetal deaths and 54% maternal deaths in a study by Banait et al. [17,25]

The mechanism underlying these outcomes is not known, but vertical transmission might be a cause. This was not studied by us, in a study; vertical transmission of HEV was detected in 5 newborns whose mothers had developed hepatitis during an epidemic of waterborne HEV infection. Vertical transmission was also detected in 26 cases of HEV RNA-positive women by testing for HEV RNA in cord blood or new born blood.[10]

Evidence assembled to date suggests that mother-to-child HEV transmission may be frequent and deleterious to the fetus and newborn in pregnancies affected by hepatitis E92].Mother to child transmission of hepatitis E virus infection was established in 50% cases in a study conducted by Singh et al.[23]

CONCLUSION

The study shows that pregnant women with jaundice and acute viral hepatitis due to hepatitis E virus infection had a high mortality rate especially during third trimester and postpartum period. Also they had poor obstetric and fetal outcome.

As we observed that the severity of infection increases with duration of gestation, it is suggested that pregnant women should be periodically screened for clinical features of acute hepatitis during antenatal visits and should be investigated for hepatitis E in endemic areas. As the disease outcome is poor in pregnant women, an early diagnosis and prompt management is the key. Pregnant women with hepatitis E should be closely

monitored for fetal well-being and signs of fetal distress, as this disease also adversely affect the fetal outcome.

As rightly said prevention is better than cure, there should be emphasis on sanitation, personal hygiene, hand washing etc.to prevent the pregnant females from acquiring infection during the antenatal visits especially in the endemic areas.

The vaccine against hepatitis e has been developed and being marketed in china, with India being an endemic area for hepatitis e with so much mortality it should be considered as an option in future.

More research is required on pathogenesis of hepatitis E in pregnancy and also on management of pregnant females with hepatitis e as these still remains unclear.

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